



HLA-A*24:07 as a potential biomarker for carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis in Filipino patients

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Aim: A case-control study was conducted in Filipino patients to determine the association between HLA alleles and carbamazepine-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). **Materials & methods:** A retrospective review of medical records and data collection were performed. A total of 10 carbamazepine-induced SJS/TEN cases and 40 tolerant controls were recruited. Genomic DNA extracted from saliva samples was genotyped. Statistical analysis was done. **Results:** The HLA-B75 serotype ($p = 0.003$; odds ratio [OR] = 13.8; 95% CI = 2.5–76.8), *HLA-B*15:21* ($p = 0.041$; OR = 4.7; 95% CI = 1.1–20.8) and *HLA-A*24:07* ($p = 0.032$; OR = 6; 95% CI = 1.2–30.7) were significantly associated with carbamazepine-induced SJS/TEN. **Conclusion:** The HLA-B75 serotype, *HLA-B*15:21* or *HLA-A*24:07* may be used for pharmacogenetic screening prior to prescribing carbamazepine in Filipinos.

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Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous disorders with a high mortality rate. These disorders are usually drug induced with carbamazepine as one of the most common culprit drugs. It is now known that the *HLA-B*15:02* allele is strongly associated with carbamazepine-induced SJS/TEN in Asians but not in Koreans, Japanese and Caucasians. The association is ethnicity/race specific. Therefore, a study was conducted to describe the clinical characteristics of Filipino patients with carbamazepine-induced SJS/TEN and determine the association of HLA-A and HLA-B alleles with carbamazepine-induced SJS/TEN. Preliminary results

showed that the HLA-B75 serotype and *HLA-B*15:21* were associated with carbamazepine-induced SJS/TEN in Filipino patients [1]. Here, we report another potential predictor in addition to our previous findings.

Materials & methods

A retrospective review of medical records of patients diagnosed with carbamazepine-induced SJS/TEN and admitted for the period of 2000–2018 in the University of the Philippines, Philippine General Hospital was conducted. The clinical and histopathological diagnosis of SJS/TEN was confirmed by both an allergologist and a dermatologist. Drug causality assessment using the Naranjo algorithm was performed. Filipino patients aged 18–59 years with diagnosis of carbamazepine-induced SJS/TEN were recruited as cases. Epileptic patients who had been taking carbamazepine for at least 3 months without SJS/TEN were recruited as tolerant controls. Patients with unconfirmed diagnosis of carbamazepine-induced SJS/TEN, and with suspected erythema multiforme major (occurs after infections, especially herpes simplex and mycoplasma) were excluded in the study. Patients who were unwilling to participate in the study were also excluded. The case:control ratio was 1:4. Pairing of cases and tolerant controls by age (± 5 years) was done. The patients were recruited at the Allergy and Immunology Clinic and the Epilepsy Clinic, Department of Medicine of University of the Philippines, Philippine General Hospital.

Genomic DNA was extracted from saliva samples following the prepIT-L2P protocol (DNA Genotek, ON, Canada). Genotyping was performed by employing allele-specific PCR and by using the WAKFlow Typing kit (Wakunaga Pharmaceutical Co., Hiroshima, Japan). The Hardy–Weinberg equilibrium test was performed. The Stata version 14 (StataCorp LLC, TX, USA) was used in the statistical analysis. The strength of association was expressed as odds ratio with 95% CI. The level of significance was set at *p* value of less than 0.05. Bonferroni adjustments were done. The materials and methods used are fully described in our previous publication [1].

Results

A total of 10 patients with carbamazepine-induced SJS/TEN and 40 tolerant controls were included in this study. Four cases were classified as SJS, one case as TEN and five cases as SJS-TEN overlap. Skin biopsy was performed in eight cases only. The results correlated with the clinical presentation of SJS and TEN.

In all cases, a total score of 7 was obtained for carbamazepine in drug causality assessment using the Naranjo algorithm. It means that cutaneous adverse reactions were probably due to the carbamazepine treatment.

Table 1 describes the characteristics of all patients included in the study. Among cases, 30% were female and the median age was 33 (range: 23–56 years old). Among controls, 62.50% were female and the median age was 34 (range: 19–58 years old). Majority of the participants came from Luzon (80% for cases and 92.50% for controls) and were pure Filipinos (90% for both groups). For both groups, most were nonsmokers (70% for cases and 85% for controls) and were nonalcohol drinkers (50% for cases and 75% for controls). Only two patients were given carbamazepine for indications other than epilepsy and only three patients had history of drug allergies. The median dose of carbamazepine for both groups was 400 mg/day (range: 200–1000 mg/day). With regards to duration of carbamazepine exposure, controls had significantly longer days of drug use (median: 1096 days, range: 121–3651) when compared with cases (median: 14, range: 12–68; *p* = 0). No other significant differences were seen between the two groups in terms of patient characteristics. Also, univariate logistic regression analysis showed that none of the patient characteristics were significantly associated with having SJS/TEN.

Table 2 describes the association between carbamazepine-induced SJS/TEN and serotypes/alleles, whereas Table 3 shows the haplotype information of HLA-A and HLA-B in the case and control groups. The prevalence of HLA-B75 serotype among cases (8/10, 80%) was significantly higher than that of the control group (9/40, 22.50%; *p* = 0.001). The prevalence of *HLA-B*15:21* allele among cases (5/10, 50%) was significantly higher than that of the control group (7/40, 17.50%; *p* = 0.046). Also, the prevalence of *HLA-A*24:07* allele among cases (4/10, 40%) was significantly higher than that of the control group (4/40, 10%; *p* = 0.041). No other significant differences were observed between the two groups in terms of alleles. For *HLA-B*15:02*, there was no significant difference in the prevalence of allele between the case and control groups (*p* = 0.086).

Of all the tested alleles, only the HLA-B75 serotype, *HLA-B*15:21* and *HLA-A*24:07* allele were significantly associated with having SJS/TEN. Patients who tested positive with the HLA-B75 serotype had 13.8-times higher risk of having SJS/TEN when compared with patients who tested negative (95% CI: 2.5–76.8; *p* = 0.003). Patients who tested positive with *HLA-B*15:21* allele had 4.7-times higher risk of having SJS/TEN when compared with patients who tested negative (95% CI: 1.1–20.8; *p* = 0.041). Patients who tested positive with *HLA-A*24:07* allele had six-times higher risk of having SJS/TEN when compared with patients who tested negative (95% CI: 1.2–

Table 1. Clinico-demographic characteristics of cases and controls.

Characteristics	Cases (n = 10)	Controls (n = 40)	Fisher's exact test or Mann–Whitney U test	Univariate logistic regression	
			p-value	p-value	OR (95% CI)
Age			0.961 ^{††}	0.985	1 (0.943–1.062)
Range	23–56	19–58			
Mean ± SD	35.90 ± 12.49	35.82 ± 11.68			
Median	33	34			
Age [†]			NA	NE	NE
Range	16–54	NA			
Mean ± SD	32.2 ± 12.55	NA			
Median	32	NA			
Sex			0.084	0.075	2.89 (0.871–17.365)
Female	3 (30%)	25 (62.50%)			
Male	7 (70%)	15 (37.50%)			
Birthplace			0.172	0.154	4.62 (0.564–37.908)
Luzon	8 (80%)	37 (92.50%)			
Visayas	2 (20%)	2 (5%)			
Mindanao	0 (0%)	1 (2.50%)			
Racial history			1	1	1 (0.993–10.073)
Pure Filipino [‡]	9 (90%)	36 (90%)			
Mixed Filipino [§]	1 (10%)	4 (12.50%)			
Carbamazepine					
Indication			0.037 ^{§§}	NE	NE
Epilepsy	8 (80%)	40 (100%)			
Mood stabilization	1 (12.50%)	0 (0%)			
Neuropathic pain	1 (12.50%)	0 (0%)			
Initial dose (mg/day)			0.242 ^{††}	0.170	0.99 (0.989–1.002)
Range	200–400	200–1000			
Mean ± SD	340 ± 96.61	410 ± 154.91			
Median	400	400			
Final dose [¶] (mg/day)			NA	NE	NE
Range	200–400	NA			
Mean ± SD	360 ± 84.33	NA			
Median	400	NA			
Duration of exposure (day)			0 ^{††§§} NE	NE	NE
Range	12–68	121–3651			
Mean ± SD	25.8 ± 18.90	1271.45 ± 1146.30			
Median	14	1096			
Index day [#]			NA	NE	NE
Range	8–65	NA			
Mean ± SD	24.10 ± 18.61	NA			
Median	12.5	NA			
Concurrent medications ^{††}			NA	NE	NE
Range	0–5	NA			

[†] Age at development of cutaneous adverse reactions.
[‡] Pure Filipino = none of the parents and grandparents came from other races.
[§] Mixed Filipino = at least one grandparent came from other race.
[¶] Final dose = dosage at which cutaneous adverse reactions occurred.
[#] Index day = period from the first day of taking carbamazepine to the day of onset of signs and symptoms of cutaneous adverse reactions.
^{††} Concurrent medications: drugs that were co-administered with carbamazepine no more than 3 months prior to the onset of cutaneous adverse reactions.
^{§§} Mann–Whitney test was performed.
^{§§} Statistically significant.
NA: Not applicable; NE: No entry; OR: Odds ratio; SCAR: Severe cutaneous adverse reaction; SJS/TEN: Stevens–Johnson syndrome/toxic epidermal necrolysis.

Table 1. Clinico-demographic characteristics of cases and controls (cont.).

Characteristics	Cases (n = 10)	Controls (n = 40)	Fisher's exact test or Mann-Whitney U test	Univariate logistic regression	
			p-value	p-value	OR (95% CI)
Mean ± SD	1.11 ± 1.66	NA			
Median	0	NA			
Drug allergies			1	NE	NE
Yes	0 (0%)	3 (7.50%)			
No	10 (100%)	37 (92.50%)			
Type of SCAR			NA	NE	NE
SJS	4 (40%)	NA			
TEN	1 (10%)	NA			
SJS-TEN overlap	5 (50%)	NA			
Smoking			0.358	0.279	2.42 (0.487–12.113)
Smoker	3 (30%)	6 (15%)			
Nonsmoker	7 (70%)	34 (85%)			
Alcohol use			0.143	0.132	3 (0.717–12.553)
Alcohol drinker	5 (50%)	10 (25%)			
Nonalcohol drinker	5 (50%)	30 (75%)			

† Age at development of cutaneous adverse reactions.

‡ Pure Filipino = none of the parents and grandparents came from other races.

§ Mixed Filipino = at least one grandparent came from other race.

¶ Final dose = dosage at which cutaneous adverse reactions occurred.

* Index day = period from the first day of taking carbamazepine to the day of onset of signs and symptoms of cutaneous adverse reactions.

†† Concurrent medications: drugs that were co-administered with carbamazepine no more than 3 months prior to the onset of cutaneous adverse reactions.

‡‡ Mann-Whitney test was performed.

§§ Statistically significant.

NA: Not applicable; NE: No entry; OR: Odds ratio; SCAR: Severe cutaneous adverse reaction; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table 2. Results of HLA-A and HLA-B genotyping.

HLA	Cases (n = 10)		Controls (n = 40)		Fisher's exact test p-value	Univariate logistic regression		Multiple logistic regression	
	Frequency	%	Frequency	%		p-value	OR (95% CI)	p-value	adj OR (95% CI) [§]
A*24:07	4	40	4	10	0.041 [‡]	0.032 [‡]	6 (1.2–30.7)	0.033 [‡]	14.1 (1.2–160.6)
B*15:02	3	30	3	7.50	0.086	0.069	5.3 (0.9–31.7)	0.855	0.7 (0–11.6)
B*15:21	5	50	7	17.50	0.046 [‡]	0.041 [‡]	4.7 (1.1–20.8)	0.511	0.3 (0–6.4)
HLA-B75 serotype [†]	8	80	9	22.50	0.001 [‡]	0.003 [‡]	13.8 (2.5–76.8)	0.024 [‡]	51.2 (1.6–1581.3)

† Allele-specific PCR was performed.

‡ Statistically significant at $p < 0.05$ but not after Bonferroni correction (0.05/50 alleles: reference $p < 0.001$).§ Adjusted for *HLA-B*15:02/HLA-B*15:21/HLA-B75* serotype as potential confounder.Note: Hosmer-Lemeshow test showed a value of 1.52 ($p = 0.823$) indicating we do not reject the model. Cox and Snellen R^2 showed a value of 0.299 while Cragg and Uhler R^2 showed a value of 0.472 indicating that the model explains 30–47% of the variability of the response variable (carbamazepine-induced SJS/TEN).

adj: Adjusted; OR: Odds ratio; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

30.7; $p = 0.032$). All of the tested alleles were not significantly associated with carbamazepine-induced SJS/TEN when the Bonferroni corrected p -value (< 0.001) was used as reference.

Multiple logistic regression analysis was conducted to determine if *HLA-A*24:07* was independently associated with the outcome after controlling for HLA-B75 serotype, *HLA-B*15:02* and *HLA-B*15:21*. Results showed that *HLA-A*24:07* remained to be significantly associated with SJS/TEN (OR: 14.1; 95% CI: 1.2–160.7; $p = 0.033$). It was also observed that HLA-B75 serotype confounds the association between *HLA-A*24:07* and SJS/TEN since the OR of *HLA-A*24:07* increased to more than twice when the effect of HLA-B75 serotype was controlled. Controlling for *HLA-B*15:02* and *HLA-B*15:21* do not affect the magnitude of OR of *HLA-A*24:07*.

Discussion

The Philippines is an archipelago consisting of 7641 islands. The islands are clustered into three major island groups, namely Luzon, Visayas and Mindanao. Based on birthplace, majority of patients (80% of cases and 92.50%

Table 3. Haplotype information in cases and controls.

Participant ID	HLA-A		HLA-B		HLA-B*15:02 (PCR)	HLA-B75 Serotype (PCR)
			Case			
01-01	A*31:01	A*34:01	B*15:21	B*39:02	Negative	Positive
02-02	A*02:01	A*24:07	B*15:21	B*35:05	Negative	Positive
03-03	A*02:01	A*02:01	B*15:13	B*38:02	Negative	Negative
04-05	A*24:02	A*34:01	B*15:21	B*55:02	Negative	Positive
05-06	A*34:01	-	B*15:21	B*15:35	Negative	Positive
06-08	A*02:07	A*24:07	B*35:05	B*46:01	Negative	Negative
07-09	A*11:01	A*24:02	B*15:02	B*40:01	Positive	Positive
08-12	A*24:02	A*24:17	B*15:02	B*51:02	Positive	Positive
09-13	A*24:02	A*24:07	B*15:02	B*15:02	Positive	Positive
10-14	A*02:01	A*24:07	B*15:21	B*35:05	Negative	Positive
Control						
01-01-1	A*24:02	A*33:03	B*15:35	B*38:02	Negative	Negative
02-01-2	A*02:01	A*24:02	B*38:02	B*51:02	Negative	Negative
03-01-3	A*24:02	A*24:02	B*15:139	B*38:02	Negative	Positive
04-01-4	A*31:01	A*34:01	B*15:21	B*58:01	Negative	Positive
05-02-1	A*02:06	A*24:07	B*07:05	B*35:05	Negative	Negative
06-02-2	A*11:04	A*66:01	B*15:35	B*51:01	Negative	Negative
07-02-3	A*34:01	A*34:01	B*15:35	B*38:02	Negative	Negative
08-02-4	A*02:01	A*34:01	B*15:02	B*15:21	Positive	Positive
09-03-1	A*24:02	A*24:07	B*15:141	B*48:29	Negative	Negative
10-03-2	A*24:02	A*24:07	B*13:01	B*35:05	Negative	Negative
11-03-3	A*24:02	A*24:03	B*13:01	B*51:06	Negative	Negative
12-03-4	A*02:01	A*34:01	B*15:21	B*27:06	Negative	Positive
13-05-1	A*24:02	A*34:01	B*40:02	B*52:01	Negative	Negative
14-05-2	A*11:04	A*66:01	B*07:05	B*15:02	Positive	Positive
15-05-3	A*24:02	A*34:01	B*15:35	B*35:01	Negative	Negative
16-05-4	A*11:01	A*33:03	B*38:02	B*44:02	Negative	Negative
17-06-1	A*02:01	A*33:03	B*18:01	B*58:01	Negative	Negative
18-06-2	A*31:01	A*33:03	B*44:03	B*55:02	Negative	Negative
19-06-3	A*02:01	A*11:01	B*38:02	B*56:02	Negative	Negative
20-06-4	A*23:14	A*33:102	B*40:02	B*44:03	Negative	Negative
21-08-1	A*11:04	A*66:01	B*15:21	B*40:01	Negative	Positive
22-08-2	A*02:01	A*33:03	B*44:02	B*58:01	Negative	Negative
23-08-3	A*11:04	A*66:01	B*38:02	B*46:01	Negative	Negative
24-08-4	A*24:02	A*24:02	B*40:01	B*40:02	Negative	Negative
25-09-1	A*02:01	A*24:02	B*15:345	B*40:117	Negative	Negative
26-09-2	A*11:01	A*24:02	B*18:01	B*40:02	Negative	Negative
27-09-3	A*24:02	A*34:01	B*38:02	B*40:02	Negative	Negative
28-09-4	A*11:01	A*68:01	B*15:09	B*51:37	Negative	Negative
29-12-1	A*02:07	A*03:01	B*07:02	B*46:01	Negative	Negative
30-12-2	A*24:02	A*34:01	B*15:35	B*56:02	Negative	Negative
31-12-3	A*02:01	A*11:01	B*15:01	B*15:35	Negative	Negative
32-12-4	A*02:01	A*11:01	B*38:02	B*51:02	Negative	Negative
33-13-1	A*24:02	A*34:01	B*38:02	B*38:02	Negative	Negative
34-13-2	A*11:01	A*34:01	B*15:02	B*15:21	Positive	Positive
35-13-3	A*24:02	A*34:01	B*15:21	B*35:05	Negative	Positive
36-13-4	A*11:01	A*33:03	B*38:02	B*58:01	Negative	Negative
37-14-1	A*24:02	A*34:01	B*15:21	B*48:01	Negative	Positive
38-14-2	A*24:02	A*24:02	B*38:02	B*40:01	Negative	Negative
39-14-3	A*02:07	A*03:01	B*41:01	B*46:01	Negative	Negative
40-14-4	A*24:02	A*24:07	B*35:05	B*38:02	Negative	Negative

of controls) originated from Luzon which is the largest island group in the Philippines. Tagalog is the ethnolinguistic group with the highest population in the Philippines [2]. In this study, majority of the recruited patients belong to this ethnolinguistic group suggesting that the study population is culturally almost homogenous. However, the study population may not be representative of the Filipino population. Patient recruitment was done only in hospitals in Luzon due to logistic reasons and budget limitation.

In the case group, the age at which SJS/TEN developed ranged from 16 to 54 years old. The mean age was 32.20 ± 12.55 years and the median age was 32 years. In a study by Alvestad *et al.*, they concluded that the risk of carbamazepine-induced rash increases with age (6% in patients below 16 years, 12% in those aged 16–49 years and 19% in those aged above 50 years [3]. In terms of sex distribution, there is a male preponderance (70%) in the case group, while there is a female preponderance (62.50%) in the control group. The male preponderance observed in the case group was also noted in previous studies [4–11]. This observation is in contrast to the report of Alvestad *et al.* that females tend to be at higher risk of carbamazepine-induced rash than males, particularly in reproductive age. They suggested that this finding is due to the influence of sex hormones on T-cell populations as carbamazepine-induced rash is an immunologically T-cell-mediated reaction [3].

All included cases were pure Filipinos except for five patients (one case and four controls) who were considered as mixed Filipinos. Those patients who were considered as mixed Filipinos had Chinese, German, Indian and Spanish descent. This finding is not surprising knowing that there is diversity in the foreign influences on the Philippines that originated from different parts of Asia-Pacific region, Europe and the Americas. In addition, migrations and intermarriages are possible reasons for having a mixed race [12].

No association was found between carbamazepine-induced SJS/TEN and *HLA-B*15:02*. The SJS/TEN due to carbamazepine was associated with the HLA-B75 serotype and *HLA-B*15:21* allele. These results were consistent with our preliminary findings. Here, we reported that the carbamazepine-induced SJS/TEN was also associated with the *HLA-A*24:07* allele. The degree of association was greater in the HLA-B75 serotype as compared with the *HLA-B*15:21* and *HLA-A*24:07* alleles. Two cases tested negative for the HLA-B75 serotype. Maybe the subjects have different T-cell receptor type that is involved in the immunopathogenesis of carbamazepine-induced SJS/TEN.

The association of *HLA-A*24:07* with carbamazepine-induced SJS/TEN has been demonstrated in this study. There was no previous study on the association between the *HLA-A*24:07* allele and carbamazepine-induced SJS/TEN. To the best of our knowledge, our study is the first study to demonstrate the association of *HLA-A*24:07* and carbamazepine-induced SJS/TEN. An association of the HLA-A with carbamazepine-induced adverse drug reactions has been reported only on *HLA-A*31:01*. The *HLA-A*31:01* allele was reported to be associated with hypersensitivity reactions caused by carbamazepine, including maculopapular exanthema, hypersensitivity syndrome and SJS/TEN in Asian [4,9,13], Canadian [14] and European [15] patients. It is interesting to note that although statistical significance was not reached, one case and two controls were carriers of *HLA-A*31:01*. This finding is not surprising knowing that the Philippines was colonized and influenced by the Europeans, Americans and Japanese who were reported to be carriers of *HLA-A*31:01*.

Based on multiple regression analysis, it seems that *HLA-A*24:07* has synergistic effect with the HLA-B75 serotype. Carrying the HLA-B75 serotype and *HLA-A*24:07* may increase the risk of carbamazepine-induced SJS/TEN. This observation remains inconclusive due to the small sample size. More samples are needed to establish the aforementioned synergistic effect.

The study has limitations. The association of carbamazepine-induced SJS/TEN with *HLA-B*15:02* and the synergistic effect of the HLA-B75 serotype and *HLA-A*24:07* were not certain due to small number of carbamazepine-induced SJS/TEN patients. Severe cutaneous adverse reactions are so rare. Finding a case was challenging, most especially in a country where there is a lack of national registry for severe cutaneous adverse reaction. It is recommended that a multi-site case-control study be conducted nationwide to include cases from Visayas and Mindanao. A hospital research network must be created to facilitate referral of cases more easily.

Conclusion

In conclusion, the *HLA-A*24:07* allele may be used as a biomarker to predict susceptibility to carbamazepine-induced SJS/TEN in Filipino patients in addition to the previously reported biomarkers such as the HLA-B75 serotype and *HLA-B*15:21*. In the future, pharmacogenetic testing can be used to identify those patients at risk of carbamazepine-induced SJS/TEN, thereby allowing an individualized drug therapy to prevent the incidence of adverse drug reactions.

Summary points

Introduction

- Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life threatening and usually drug induced.
- The association between *HLA-B*15:02* and carbamazepine-induced SJS/TEN is ethnicity/race specific.
- A study was conducted to determine the association of HLA-A and HLA-B alleles with carbamazepine-induced SJS/TEN in Filipino patients.

Materials & methods

- A retrospective review of medical records was conducted.
- Drug causality assessment was performed using the Naranjo algorithm.
- A total of ten Filipino patients aged 18–59 years and diagnosed with carbamazepine-induced SJS/TEN were recruited as cases.
- A total of 40 epileptic patients who had been taking carbamazepine for at least 3 months without SJS/TEN were recruited as tolerant controls.
- Genomic DNA was extracted from saliva samples and genotyped.
- The Hardy–Weinberg equilibrium test was performed.
- Statistical analysis was done.

Results

- In all cases, a total score of 7 (probable) was obtained for carbamazepine in drug causality assessment.
- No significant differences were seen between the two groups in terms of patient characteristics, except for the duration of carbamazepine exposure.
- None of the patient characteristics were significantly associated with having SJS/TEN.
- The prevalence of the HLA-B75 serotype, *HLA-B*15:21* and *HLA-A*24:07* among cases was significantly higher than that of the control group.
- No other significant differences were observed between the two groups in terms of alleles.
- The HLA-B75 serotype, *HLA-B*15:21* and *HLA-A*24:07* were significantly associated with having SJS/TEN.
- All of the tested alleles were not significantly associated with carbamazepine-induced SJS/TEN when the Bonferroni adjustments were done.
- The HLA-B75 serotype confounds the association between *HLA-A*24:07* and SJS/TEN.

Discussion

- Majority of the recruited patients belong to the Tagalog group, which is the ethnolinguistic group with the highest population in the Philippines, suggesting that the study population is culturally almost homogenous.
- In the case group, the age at which SJS/TEN developed ranged from 16 to 54 years old. In a study by Alvestad *et al.*, they concluded that the risk of carbamazepine-induced rash increases with age.
- The male preponderance observed in the case group was also noted in previous studies. This observation is in contrast to the report of Alvestad *et al.* that females tend to be at higher risk of carbamazepine-induced rash than males, particularly in reproductive age.
- Cases who were considered as mixed Filipinos had Chinese, German, Indian and Spanish descent. This finding is not surprising knowing that there is diversity in the foreign influences on the Philippines that originated from different parts of Asia-Pacific region, Europe and the America.
- The degree of association with carbamazepine-induced SJS/TEN was greater in the HLA-B75 serotype as compared with the *HLA-B*15:21* and *HLA-A*24:07* alleles.
- Two cases tested negative for the HLA-B75 serotype. Maybe the subjects have different T-cell receptor type that is involved in the immunopathogenesis of carbamazepine-induced SJS/TEN.
- To the best of our knowledge, our study is the first study to demonstrate the association of *HLA-A*24:07* and carbamazepine-induced SJS/TEN.
- An association of the HLA-A with carbamazepine-induced adverse drug reactions has been reported only on *HLA-A*31:01*. The *HLA-A*31:01* allele was reported to be associated with hypersensitivity reactions caused by carbamazepine in Asian, Canadian and European patients.
- It is interesting to note that although statistical significance was not reached, one case and two controls were carriers of *HLA-A*31:01*. This finding is not surprising knowing that the Philippines was colonized and influenced by the Europeans, Americans and Japanese who were reported to be carriers of *HLA-A*31:01*.
- The association of carbamazepine-induced SJS/TEN with *HLA-B*15:02* and the synergistic effect of the HLA-B75 serotype and *HLA-A*24:07* were not certain due to small number of carbamazepine-induced SJS/TEN patients.

Conclusion

- The HLA-B75 serotype, *HLA-B*15:21* and *HLA-A*24:07* allele may be used as a biomarker to predict susceptibility to carbamazepine-induced SJS/TEN in Filipino patients.

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Financial & competing interests disclosure

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Ethical conduct of research

The study protocol was approved by the University of the Philippines Manila Research Ethics Board (UPMREB) with study protocol code UPMREB 2017-096-01 and by the Faculty of Dentistry and Faculty of Pharmacy Institutional Review Board, Mahidol University with reference number 0517.0319/364.

References

1. Capule F, Tragulpiankit P, Mahasirimongkol S *et al.* Association of carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis with the HLA-B75 serotype or *HLA-B*15:21* allele in Filipino patients. *Pharmacogenomics J.* 20, 533–541 (2020).
2. Lewis MP, Simons GF, Fennig CD. Ethnologue: language of the world. In: *SIL International, 2016 (19th Edition)*. (2020). <https://www.ethnologue.com/>
3. Alvestad S, Lydersen S, Brodtkorb E. Rash from antiepileptic drugs: influence by gender, age, and learning disability. *Epilepsia* 48(7), 1360–1365 (2007).
4. Hung SI, Chung WH, Jee SH *et al.* Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet. Genomics* 16, 297–306 (2006).
5. Zhang Y, Wang J, Zhao LM *et al.* Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. *Eur. J. Clin. Pharmacol.* 67, 885–887 (2011).
6. Shi YW, Min FL, Qin B *et al.* Association between HLA and Stevens-Johnson syndrome induced by carbamazepine in southern Han Chinese: genetic markers besides B*1502. *Basic Clin. Pharmacol. Toxicol.* 111, 58–64 (2012).
7. Khor AHP, Lim KS, Tan CT, Wong SM, Ng CC. HLA-B*15:02 association with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in an Indian population: a pooled-data analysis and meta-analysis. *Epilepsia* 55(11), 120–124 (2014).
8. Nguyen DV, Chu HC, Nguyen DV *et al.* HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pac. Allergy* 5, 68–77 (2015).
9. Kim SH, Lee KW, Song WJ *et al.* Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res.* 97, 190–197 (2011).
10. Kaniwa N, Saito Y, Aihara M *et al.* HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 9(11), 1617–1622 (2008).
11. Lonjou C, Borot N, Sekula P *et al.* A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet. Genomics* 18, 99–107 (2008).
12. Delfin FC. The population history of the Philippines: a genetic overview. *Philippine Studies: Historical and Ethnographic Viewpoints* 63(4), 449–476 (2015).
13. Niihara H, Kakamu T, Fujita Y, Kaneko S, Morita E. HLA-A31 strongly associates with carbamazepine-induced adverse drug reactions but not with carbamazepine-induced lymphocyte proliferation in a Japanese population. *J. Dermatol.* 39, 594–601 (2012).
14. Amstutz U, Ross CJD, Castro-Pastrana LI *et al.* HLA-A*31:01 and HLA-B*15:02 as genetic markers for carbamazepine hypersensitivity in children. *Clin. Pharmacol. Ther.* 94(1), 142–149 (2013).
15. McCormack M, Alfirevic A, Bourgeois S *et al.* HLA-A*31:01 and carbamazepine-induced hypersensitivity reactions in Europeans. *N. Engl. J. Med.* 364, 1134–1143 (2011).